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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/921,157	08/02/2001	Antonello Covacci	CHIR-0315	7773

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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	12

DATE MAILED: 10/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/921,157	Covacci et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 6, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *38-44* is/are pending in the application.

4a) Of the above, claim(s) *41-43* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *38-40 and 44* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. *08/256,848* .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *7.*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Preliminary Amendments

1) Acknowledgment is made of preliminary amendments filed 02/27/02, 08/02/01 and 08/06/02 (paper no. 6, 8 and 11). With these, Applicants have amended the specification.

Sequence Listing

2) Acknowledgment is made of Applicants' submission of the raw sequence listing and CRF which has been entered on 08/15/01 (paper no. 2).

Information Disclosure Statement

3) Acknowledgment is made of Applicants' information disclosure statement filed 09/27/01 (paper no. 7). The information referred to therein has been considered and a signed copy of the same is attached to this Office Action (paper no. 12).

Election

4) Acknowledgment is made of Applicants' election, with traverse, of invention I, claims 38-40 and 44, filed 08/06/02 (paper no. 11) in response to the restriction requirement mailed 07/08/02 (paper no. 9).

The Applicants' traversal is on the grounds that examination of claims of inventions I and II would not impose a serious burden to the Examiner.

The Applicants' argument has been carefully considered, but is not persuasive. As clearly set forth in paragraph 4 of the restriction requirement mailed 07/08/02 (paper no. 9), inventions I and II are related as product and process of making the product of invention I. M.P.E.P 806.05(f) permits the Office to separate the product from the process of making the product by showing that the process of making the vaccine can be used to make a materially different product, such as, an *in vitro* diagnostic reagent or composition. While the product belongs to class 424, the process of invention II is classified under a different class 435. Therefore, a search performed for the product would not be co-extensive to the process of invention II. For these reasons, the restriction requirement mailed 07/08/02 is maintained and is hereby made FINAL.

Status of Claims

5) Claims 1-37 have been canceled via the amendment filed 08/02/01.

New claims 38-44 have been added via the amendment filed 08/02/01.

Claims 41-43 have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

The elected claims 38-40 and 44 are under examination. An Action on the Merits for these claims is issued.

Priority

6) This application is a Continuation application of SN 09/360,934 filed 07/26/99, *now pending*, which is a Divisional application of SN 08/471,491, filed 06/06/95, now US patent 6,090,611, which is a Divisional application of SN 08/256,848, filed 10/21/94, now abandoned, which is a national stage application of PCT/EP93/00472, filed 03/02/93 and PCT/EP93/00158, filed 01/25/93. The instant application claims the priority benefit to the Italian application, SN FI 92A000052, filed 03/02/92.

Drawings

7) The drawings are objected to under 37 C.F.R 1.84 because of the reasons set forth by the Draftsperson in the attached Form PTO 948 (paper no. 12). Correction is required. Applicants are asked to note the changes effected 03 May 2001, particularly the changes to the 'Timing of Corrections':

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85; 1097 O.G. 36

New formal drawings must be filed with the changes incorporated therein. The art unit number, application number (including series code) and number of drawing sheets should be written on the reverse side of the drawings. Applicant may delay filing of the new drawings until receipt of the "Notice of Allowability" (PTOL-37 or PTO-37). If delayed, the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability" to avoid extension of time fees. Extensions of time may be obtained under the provisions of 37 C.F.R 1.136(a) for filing the corrected drawings (but not for payment of the issue fee). The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the three month shortened statutory period set in the "Notice of Allowability" (PTO-37). Within that three month period, two weeks should be allowed for review of the new drawings by the Office. If a correction is determined to be unacceptable by the Office, Applicant must arrange to have an acceptable correction re-submitted within the original three month period to avoid the necessity of obtaining an extension of time with extension fees. Therefore, applicant should file corrected drawings as soon as possible.

Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

Specification - Informalities

8) The specification is objected to for the following reasons:

(a) The amendment introduced to the first paragraph of the specification does not accurately reflect the current issued status of the earlier filed application(s) as indicated above in italicized letters under 'Priority'. Amendment to the first paragraph of the specification is needed to reflect this.

(b) The use of the trademarks in the instant specification has been noted in this application. For example, see page 39, last paragraph: "Tween 80 "; "Span 85" and "Squalene". Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole

specification and make necessary changes wherever trademark recitations appear.

(c) On page 61, lines 4-6, the address of the American Type Culture Collection is incorrect. Effective 23 March 1998, ATCC has a new address: 10801 University Boulevard, Manassas, VA 20110-2209. Amendment to the specification is suggested to reflect this. It is suggested that Applicants examine the whole specification to make similar correction to the address, wherever it appears.

(d) The amendment filed 08/06/02 is objected to under U.S.C. § 132 because it introduces new matter into the disclosure. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: "initiation sites. The expression of a portion of the CAI antigen by clone 57/D suggests". Applicants point to page 53, lines 31-38 and state that this part of the specification provides support for the added limitations. However, there appears to be no descriptive support for the added limitations and for clone 57/D. Applicants are required to cancel the new matter in the response to this Office Action.

Double Patenting Rejection(s)

9) The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970) and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 C.F.R 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R 3.73(b).

Claim 44 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 63-66, 72-75, 84-86 and 93-101 of the co-pending application, SN 09/360,934. Claim 38 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 63-66, 75, 84-86, 93, 94 and 97-101 of the co-pending application, SN 09/360,934. Although the conflicting claims are not identical, they are not patentably distinct from each other because the product(s) claimed in the instant claims are encompassed in the scope of the claims of the above-identified co-pending application.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

10) Claims 38-40 and 44 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 38 is vague in the recitation "polypeptide comprising SEQ ID NO: 3" without reciting that the SEQ ID NO: 3 represents an amino acid sequence. In order to distinctly claim the subject matter of the instant invention, it is suggested that Applicants replace the recitation with --polypeptide comprising the amino acid sequence of SEQ ID NO: 3--.

(b) Claims 38 and 44 are vague and indefinite in the use of the abbreviated recitation: "CT" in the claim language. It is suggested that the abbreviation be recited as a full terminology at first occurrence in the base claim, with its abbreviated recitation retained in parentheses.

(c) Claim 39 is vague and/or confusing in the recitation: "exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity", because it is unclear what function does not contribute, or does show substantially reduced contribution to what toxicity. Since the phrase does not appear to have been defined within the instant specification, it is not clear whether this toxicity represents cytotoxicity, endotoxicity, exotoxicity, cell-vacuolizing toxicity, or any other type of toxicity.

(d) Claims 38 and 44 are vague and indefinite in the recitation: "substantially no toxicity" and "substantially reduced toxicity", because it is unclear what degree of toxicity qualifies as substantially no toxicity or substantially reduced toxicity. The specification does not

appear to provide a standard for ascertaining the requisite degree of toxicity that qualifies as "substantially no toxicity" and "substantially reduced toxicity". The metes and bounds of the claims are indeterminate.

(e) The recitation "can induce" in claims 38, 39 and 44 renders the claims indefinite, because it is unclear whether the limitations following this phrase are part of the claimed invention. The limitation "can induce" is not a positive and/or definite recitation of further steps and as such renders the claims indefinite.

(f) Claim 39 is vague and indefinite in the recitation "fragment thereof", because it is unclear what is encompassed in this limitation, or how many or what amino acid residues are encompassed in the 'fragment'.

(g) Claim 40, which depends directly or indirectly from claim 38, is also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, because of the indefiniteness or vagueness, identified above in the base claim.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

11) Claims 39 and 40 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Instant claims encompass a prophylactic or therapeutic vaccine comprising an immunologically effective amount of a fragment of the CAI antigen of *H. pylori* comprising "at least ten amino acids" or "at least fifteen amino acids" which fragments have the capacity to induce antibodies to *H. pylori* and exhibit no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity. Claims do not identify the CAI antigen or its fragment by a SEQ ID number. A review of the instant specification shows that Applicants were not in possession of these fragments possessing the recited properties. Instant claims recite insufficient relevant identifying characteristics of the claimed fragment of the CAI antigen. The instant specification provides inadequate written description to allow one skilled in the art to predictably determine the structural composition of the fragment(s). The precise structural composition of

the claimed CAI comprising at least 10 or 15 amino acids is not adequately described such that one of ordinary skill in the art could produce such CAI polypeptide fragments which exhibit no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity and which can be used to induce the production of antibodies to *H. pylori*. There is a lack of written description as to which specific 10 or 15 contiguous or discontiguous amino acid residues of the CAI antigen are encompassed in the claimed polypeptide fragment. It is uncertain whether retention of any 10 or 15 contiguous or discontiguous amino acid residues from any part of the CAI antigen (i.e., terminal or central parts) would yield a polypeptide that would have the expected immunogenic functions and the capacity to exhibit no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity. In view of the level of knowledge and skill in the art, one skilled in the art would not recognize from the instant disclosure that Applicants were in possession of the recited CAI fragments having the recited properties. See Written Description Requirement published in *Federal Register*, Vol. 66, No. 4, Friday, 05 January 2001, Notices, p. 1099-1111.

12) Claims 38-40 and 44 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

Instant claims encompass a *Helicobacter pylori* CT polypeptide and a CAI polypeptide or a CAI fragment comprising "at least ten" or "at least fifteen" amino acids, which polypeptide(s)

have the ability to induce the production of antibodies to *H. pylori* while exhibiting no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity, or substantially no or reduced toxicity. The scope of the claims encompasses ten amino acid-long or fifteen amino acid-long fragments of the recombinant or non-recombinant CAI antigen which concurrently have the ability to exhibit substantially no or reduced toxicity, the ability to induce antibodies against *H. pylori* and the ability to serve as a therapeutic or prophylactic vaccine. However, the instant specification does not provide enablement for such CT and CAI polypeptides or CAI fragments having "at least ten" or "at least fifteen" contiguous or discontiguous amino acids of the CAI antigen and having the recited characteristics. The precise structural composition of the claimed CAI comprising at least 10 or 15 amino acids is not disclosed such that one of ordinary skill in the art could produce such polypeptides which exhibit no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity and which can be used to induce the production of therapeutic or prophylactic antibodies to *H. pylori*. There is a lack of disclosure as to which specific 10 or 15 contiguous or discontiguous amino acid residues of the CAI antigen are encompassed in the claimed polypeptide(s). It is uncertain whether retention of any 10 or 15 contiguous or discontiguous amino acid residues from any part of the CAI antigen (i.e., terminal or central parts) would yield a polypeptide that would have the expected immunogenic functions and the capacity to exhibit no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity. Furthermore, it is not predictable that any 10 or any 15 amino acids in the CAI polypeptide would retain *H. pylori*-specificity while conferring immunogenicity and non-toxicity or substantially reduced toxicity to the polypeptide. The state of the art on bacterial polypeptides demonstrates the unpredictability associated with the presence of an epitope on any 10 amino acid-long fragment from any part of a given bacterial polypeptide antigen. Therefore, the immunogenicity of such a polypeptide antigen fragment, let alone its non-toxicity and *H. pylori*-specificity, is non-predictable. For example, McGuinnes *et al.* (WO 90/06696) clearly demonstrate that portions of an immunodominant bacterial polypeptide comprising ten contiguous amino acid residues from any random parts of the whole polypeptide molecule do not contain the antigenic epitope(s) that are recognized by the

bactericidal or protective antibodies (see entire document, especially Figure 5). Every 10-mer portions on this bacterial polypeptide did not contain such epitope(s) indicating that the prophylactic (protective) or therapeutic efficacy of any fragments from any portion of a bacterial polypeptide antigen is not a predictable event. In the instant case, it is also required that the recited fragments remain substantially non-toxic or less toxic in addition to carrying the protective epitope(s). Therefore, a 10-mer fragment or a 15-mer fragment from any portion of the instantly claimed *H. pylori* CAI polypeptide cannot be assumed to contain or retain *H. pylori*-specific antigenic determinants that are needed for immunogenicity, or that induce prophylactic or therapeutic immune response and at the same time remain non-toxic or less toxic. Clearly, the specification does not teach fragments comprising ten or fifteen amino acids of the CAI antigen which are non-toxic or substantially less toxic, *H. pylori*-specific and at the same time, effective for use as a prophylactic or therapeutic vaccine against *H. pylori* infection. Without a disclosure of the specific amino acid residues contained within the claimed at least 10-mer or at least 15-mer polypeptide, one of ordinary skill in the art cannot be sure of the sequences embraced by the claims and would not be able to make and use those polypeptide sequences or fragments, as recited in the instant claims, for a prophylactic or therapeutic purpose, without undue experimentation.

The instant specification does not reasonably enable the CT polypeptide antigen of *H. pylori* which "exhibits no toxicity, or substantially reduced toxicity" while concurrently having the ability to "induce the production of antibodies to *H. pylori*". The instant specification does not reasonably enable the recited CAI antigen of *H. pylori* or a 10-mer or 15-mer fragment thereof comprising at least ten or fifteen amino acids which "exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity" and concurrently has the ability to "induce the production of antibodies to *H. pylori*". The claimed *H. pylori* CT polypeptide encompasses recombinant and non-recombinant CT. The broadly recited toxicity encompasses all types of toxicity, including cytotoxicity or cell vacuolizing/vacuolating activity. The last paragraph on page 5 of the specification expressly states that CT is cytotoxic in that it causes vacuolation and death of a number of eukaryotic cell types. The vaccine, as claimed in the

instant claims, comprises another polypeptide, such as, the CAI polypeptide or a 10mer or 15-mer fragment thereof. The specification on page 50, below the side heading "a. Immunodominance and cytotoxicity", teaches the vacuolizing cytotoxic activity of the non-recombinant CAI antigen samples on HeLa cells. The same is reflected in the state of the art. For instance, Oderda *et al.* (*Eur. J. Gastroenterol and Hepatology*, 5 (9): 695-699, 1993) teach the cytotoxin-associated p130 protein to be "strongly associated with cytotoxicity" (see page 695, left column). Given the lack of enablement in the instant the specification for a recombinant or non-recombinant CAI antigen or its 10-mer or 15-mer fragments, having no toxicity or having substantially reduced 'toxicity', the description from the specification and/or the state of the art for the CAI is contrary to the limitation in the claims: "exhibits no ..... toxicity" or "substantially reduced functional toxicity". There is no teaching in the instant specification as to how to make and use CT that exhibits no or substantially reduced functional contribution to toxicity and/or non-toxic or substantially less toxic CAI polypeptide as a therapeutic or prophylactic vaccine candidate.

The line bridging pages 38 and 39 describes that the instantly claimed vaccine may either be "prophylactic (to prevent infection) or therapeutic (to treat disease after infection)". Therefore, the claimed prophylactic vaccine should prevent *H. pylori* infection when administered before a subject acquires the infection, and the claimed therapeutic vaccine should have the capacity to treat *H. pylori* infection when administered after a subject acquires the infection. The instant specification on page 50, lines 15 and 16 indicates that the non-recombinant polypeptide was used to immunize rabbits. However, neither a recombinant or non-recombinant CT, nor a CAI polypeptide or ten amino acid- or fifteen amino acid-long fragments of the CAI polypeptide, are enabled as prophylactic vaccines capable of preventing *H. pylori* infection, or as therapeutic vaccines capable of treating an already existing *H. pylori* infection. The instant specification lacks *in vivo* evidence demonstrating the prophylactic or therapeutic efficacy of the claimed vaccine with or without the second polypeptide, or any *in vitro* evidence that is predictive of, or correlative with prophylactic and therapeutic efficacy of the vaccine. Without an enabling disclosure and a concrete demonstration that the claimed polypeptide(s), including any fragment comprising at least 10 or 15 amino acid residues of the CAI polypeptide, prevents a *H. pylori*

infection, or treats an already existing *H. pylori* infection, one of ordinary skill in the art cannot practice the invention as claimed. A "vaccine", by definition, is required to stimulate a 'protective immune response'. A mere mention in the specification that a bacterial polypeptide(s) is meant for use as a prophylactic or therapeutic vaccine is insufficient to meet the enablement provisions of 35 U.S.C. 112, first paragraph and to predict the protective capacity of the polypeptide antigen *H. pylori*. While the immunogenicity of bacterial polypeptides is generally predictable, their protective, prophylactic or therapeutic efficacy is not. It is known in the art that not all bacterial polypeptide antigens induce protective immune response, i.e., bactericidal, neutralizing or opsonophagocytic antibodies or protective cellular immune responses.

Clearly, the protective (i.e., therapeutic or prophylactic) capacity of the polypeptide of SEQ ID NO: 3 or of a recombinant *H. pylori* CT against cytotoxigenic or non-cytotoxigenic pathogenic *H. pylori*, has not been enabled or established. The specification fails to teach that the antibody response to the polypeptide of SEQ ID NO: 3 and/or a CAI polypeptide or a 10-mer or 15-mer fragment of the CAI thereof, would serve as a therapeutic or prophylactic vaccine composition, i.e., has the capacity to confer a protective immune response against infection by an isolate of *H. pylori*. Vaccines are required to elicit an immunoprotective response in the vaccinated host, as opposed to having a mere capacity to serve as antigens with specific binding abilities, or as immunogens with an ability to elicit an antibody or immune response. The art of vaccines recognizes the unpredictability associated with whether an antigen or immunogenic component derived from a microbial pathogen is immunoprotective. For instance, Ellis RW (*Vaccines*, (Eds) Plotkin *et al.*, W.B. Saunders Company, Philadelphia, Chapter 29, 1988, see page 571, second full paragraph) reflects this problem in the teaching that the key to the problem of vaccine development "is the identification of that protein component of a ..... microbial pathogen that itself can elicit the production of protective antibodies ..... and thus protect the host against attack by the pathogen". In the instant case, the specification fails to teach or show that the recombinant or non-recombinant polypeptide of the amino acid sequence SEQ ID NO: 3, alone or in combination with the CAI polypeptide or a 10-mer or 15-mer fragment of the CAI antigen, does in fact induce an immune response that is protective against *H. pylori*. The

selection of an immunogenic component that is protective from a myriad of immunogenic components present on the microbial surface, or produced by a microbial pathogen, cannot be accomplished with a predictable precision, without undue experimentation. There is absolutely no evidence or guarantee that the polypeptide of SEQ ID NO: 3 of *H. pylori*, or a recombinant CT would be therapeutic, prophylactic or protective against *H. pylori*. The specification fails to teach that the mere presence of antibodies which bind to the polypeptide of SEQ ID NO: 3 or a recombinant CT and/or a CAI antigen or a 10-mer or 15-mer fragment thereof, provides protection from infection by *H. pylori*. There is no evidence within the instant specification that the claimed CT polypeptide and/or CIA polypeptide is able to perform as a vaccine by conferring protection, or eliminating the disease, or lowering the morbidity and/or mortality of the disease caused by *H. pylori*.

Furthermore, without specific guidance and/or a precise description, one of ordinary skill in the art cannot envisage which 10-mer or 15-mer parts on the recombinant or non-recombinant CAI polypeptide contribute to what 'toxicity'. Whether or not such products have functional or biologic capacity to be immunogenic, *H. pylori*-specific, prophylactic and therapeutic is unknown and unpredictable, and would have required undue experimentation to produce. Since which 10-mer or 15-mer fragment of the CAI antigen would retain *H. pylori* specificity and serve as a prophylactic or therapeutic vaccine against *H. pylori* infection while at the same time exhibiting no or substantially reduced functional contribution to toxicity, could be predicted, and since the epitopes on the CAI responsible for therapeutic or prophylactic properties are not known or identified, one of ordinary skill would be forced into experimentation that is undue.

Absent a showing that a therapeutic or prophylactic vaccine composition comprising a recombinant CT or a polypeptide of SEQ ID NO: 3, is effective in inducing a 'protective' immune response against *H. pylori* before or after a subject gets infected with *H. pylori*, the instantly claimed product is not enabled. In view of the lack of teachings within the instant specification, the lack of specific guidance, the breadth of the claims, the lack of working example, the functional unpredictability recognized in the state of the art, and the quantity of the experimentation required, undue experimentation would have been required by one of ordinary

skill in the art to reproducibly practice the full scope of the invention, as claimed.

Relevant Prior Art

13) The prior art made of record and not currently relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Cover *et al.* (*J. Biol. Chem.* 267: 10570-10575, 192, Applicants' IDS) teach the purification of a vacuolating toxin from the culture supernatant of *Helicobacter pylori* (see entire document).

Objection(s)

14) In lines 2 and 3 of claim 39, for clarity, it is suggested that Applicants replace the recitation: "cytotoxin associated immunodominant .... antigen" with --cytotoxin-associated immunodominant .... antigen--.

Remarks

15) Claims 38-40 and 44 stand rejected.

16) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

17) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

September, 2002

S. DEVI, PH.D.
PRIMARY EXAMINER